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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MARSHALL, GERSTEIN & BORUN LLP
6300 SEARS TOWER
233 S. WACKER DRIVE
CHICAGO, IL 60606

EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,674	WHITLEY ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 12/20/04 has been entered. Claim 32 has been canceled and new claim 33 has been added. Claims 1-31 and 33 are currently pending and under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

Claim Rejections - 35 USC § 102

The rejection of claims 1-4, 7-8, 12-21, 24-26, 31 and 32 under 35 U.S.C. 102(a) as being anticipated by Andreansky et al. (1998) Gene Therapy, Vol. 5, 121-130, is withdrawn in view of applicant's cancellation of claim 32 and amendments to claims 1-4, 7-8, 12-21, 24-26 and 31 which now recite that the HSV expresses only one $\gamma_1$34.5 gene copy.

Claim Rejections - 35 USC § 103

The rejection of claims 5, 6, 22 and 23 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,379,674 B1 (4/30/02), hereafter referred to as Rabkin et al. in view of U.S. Patent No. 5,328,688 (7/12/94), hereafter referred to as Roizman '688., is withdrawn in view of

applicant's amendments to the claims which now recite that the HSV expresses only one $\gamma_1$34.5 gene copy.

The rejection of claims 1, 9-11, 19, and 27-29 under 35 U.S.C. 103(a) as being unpatentable over Andreansky et al. (1998) Gene Therapy, Vol. 5, 121-130 **or** U.S. Patent No. 6,379,674 B1 (4/30/02), hereafter referred to as Rabkin et al., in view of U.S. Patent No. 5,641,651 (6/24/97), hereafter referred to as Roizman '651, is withdrawn in view of applicant's amendments to the claims which now recite that the HSV expresses only one $\gamma_1$34.5 gene copy.

Claim Rejections - 35 USC § 112

The rejection of claims 19-31 under 35 U.S.C. 112, first paragraph, for scope of enablement is withdrawn in view applicant's amendments which require new grounds of rejection under 35 U.S.C. 112, first paragraph, for lack of enablement. See below.

Applicant's amendments to the claims have resulted in the following new grounds of rejection.

Claims 1-31 and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The previous office action indicated that the specification, while being enabling for methods of treating neoplastic disease of the central nervous system comprising administering to a target tumor a recombinant herpes simplex virus incapable of expressing an active $\gamma_1$34.5 gene product and comprising an expressible DNA encoding IL-4, does not reasonably provide enablement for said methods wherein the recombinant HSV encodes a cytokine other than IL-4. The claims as amended now recite wherein the recombinant HSV expresses only one $\gamma_1$34.5 gene product instead of the previous limitation wherein the HSV was incapable of expressing active $\gamma_1$34.5 gene product. The identified scope of enablement is therefore outside of the scope of the claims as amended. The specification fails to provide an enabling disclosure for making a recombinant HSV which expresses only one $\gamma_1$34.5 gene product and further fails to provide an enabling disclosure for treating any neoplastic disease comprising administering to a target tumor a recombinant HSV which expresses only one $\gamma_1$34.5 gene product and which further comprises an expressible cytokine-encoding DNA.

The specification does not provide an enabling disclosure for making a recombinant HSV which expresses only one $\gamma_1$34.5 gene product and which further comprises an expressible cytokine-encoding DNA. As disclosed in the specification, herpes simplex virus contains two copies of the $\gamma_1$34.5 gene due to its presence in the inverted terminal repeat. The specification is specifically directed to the production and use of HSV which are incapable of expressing active $\gamma_1$34.5 gene product, and provides examples of HSV in which both copies of the $\gamma_1$34.5 gene are mutated or deleted. The specification only contains a single sentence, on page 9, lines 11-12, which refers to an HSV which expresses only one $\gamma_1$34.5 gene copy. This sentence reads, "Also

encompassed by the invention are viruses which express only one copy of the $\gamma_1$34.5 genes". However, the specification provides no guidance as to how to selectively inactivate only one copy of the $\gamma_1$34.5 genes present in the inverted terminal repeats. Since the genes are present in the inverted terminal repeats, which are identical in sequence, the specification does not provide any guidance for how to selectively mutate one of these copies in one of the inverted repeats while leaving the other intact. Further, the art at the time of filing does not demonstrate that HSV capable of expressing only one copy of the $\gamma_1$34.5 gene were available at the time of filing. Further, the applicant is reminded that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1005 (CAFC 1997). Therefore, in the absence of any specific guidance present in the specification for methods of making an HSV in which only one copy of the $\gamma_1$34.5 gene is expressed and the further lack of guidance for making such HSV in the prior art of record, and in view of the nature of the HSV genome and the location of the $\gamma_1$34.5 gene in the inverted repeat, it would have required undue experimentation for the skilled artisan to make and use a recombinant HSV in which only one copy of the $\gamma_1$34.5 gene is expressed.

The specification further fails to provide an enabling disclosure for treating any type of tumor by administering to a target tumor a recombinant HSV which expresses only one $\gamma_1$34.5 gene product and which further comprises an expressible cytokine-encoding DNA. As noted above, the specification does not provide any guidance for making a recombinant HSV which expresses only one $\gamma_1$34.5 gene product. It is further noted that all of the working examples

describe and are directed to the use of recombinant HSV in which both copies of the $\gamma_1$34.5 gene are inactive. While the examples demonstrate that intratumoral administration of recombinant HSV in which both copies of the $\gamma_1$34.5 gene are inactive and which expresses two copies of IL-4 into glioma can have a therapeutic effect on the growth of the infected glioma, the examples do not provide any evidence for anti-tumor effects on gliomas or any other type of tumor by administering a recombinant HSV which expresses only one $\gamma_1$34.5 gene product and which expresses IL-4 or any other cytokine. The specification teaches that HSV in which both copies of the $\gamma_1$34.5 genes are inactivated are substantially avirulent and are unable to grow in normal CNS cells but grow in CNS tumors cells. The specification does not provide any guidance or analysis of the phenotype of an HSV which expresses only one $\gamma_1$34.5 gene product. Thus, a nexus cannot be made between the results obtained between the $\gamma_1$34.5 negative HSV in the working examples and the putative HSV which express only one $\gamma_1$34.5 gene product.

Further, as noted in the previous office action, the specification's working examples demonstrate that not all cytokines have anti-tumor activity against glioma. In example 5, the specification compares intratumoral injection of $\gamma_1$34.5 negative HSV encoding IL-4 with $\gamma_1$34.5 negative HSV encoding IL-10 for the treatment of an established glioma. Figure 6 shows that while treatment with $\gamma_1$34.5 negative HSV encoding IL-4 statistically increased survival, treatment with $\gamma_1$34.5 negative HSV encoding IL-10 did not. The prior art published at the time of filing also demonstrates the failure of recombinant HSV incapable of expressing an active $\gamma_1$34.5 gene product and comprising an expressible DNA encoding IL-10 in treating gliomas in the brain (see Andreansky et al. (1998) Gene Therapy, Vol. 5, 121-130). Andreansky et al. also

teaches that while some cytokines have been shown to have anti-tumor activity against gliomas *in vivo*, other cytokines have not. Specifically, Andreansky et al. teaches that in regards to gliomas, IL-5, IL-10, and TGF-β2 fail to generate anti-tumor immune responses, lack localized tumor killing, and/or inhibit tumor immunogenicity (Andreansky et al., page 122, paragraph 1). Thus, Andreansky et al. and the working examples presented in the instant specification provide clear evidence that cytokines differ substantially in their ability to generate anti-tumor immune responses and mediate tumor killing against gliomas, and that IL-10, IL-5, and TGF-β2 do not possess anti-tumor activity against gliomas. Therefore, based on the bread of the claims, the nature of cytokines and the documented differences in their activity and ability to induce anti-tumor immunity and/or tumor killing of gliomas, and the evidence of record that cytokines such as IL-10, IL-5, and TGF-β2 do not possess anti-tumor activity against gliomas, it would have required undue experimentation for the skilled artisan to determine cytokines other than IL-4 which might have therapeutic anti-tumor activity against tumors of the CNS or any other tissue when expressed by recombinant HSV and more specifically an HSV which expresses only one $\gamma_1$34.5 gene product.

Finally, the claims as amended have been broadened to read on the treatment of any type of tumor using an HSV which expresses only one $\gamma_1$34.5 gene product and which further expresses any cytokine. The specification, while disclosing the treatment of tumors using recombinant HSV, is specifically directed to the treatment of tumors of the CNS. The specification fails to disclose any other type of tumor which may be treated using the recombinant HSV of the instant invention. As noted above, the working examples all involve the treatment of glioma, a tumor of the CNS. However, at the time of filing, Vogelstein et al.

explains, " each individual cancer arises not from a single mutation, but from the accumulation of several mutations" (Vogelstein et al. (1993) Trends in Genetics, Vol. 9(4), page 138, lines 9-11). A corollary to this principle is that each type of tumor, lung versus colon, versus lymphoid, may have different sets of mutations. In general, two major categories of mutations can be found in transformed cells, mutations in tumor suppressor genes, and mutations in oncogenes. Vogelstein et al. teach that while the mutation of the abl oncogene to c-abl can be found in many chronic myelogenous leukemias, mutations in the tumor suppressor gene APC are more common in colorectal tumors (Vogelstein et al. (1993) Trends in Genetics, Vol. 9(4), page 140, column 2, paragraphs 2-3, and page 141, column 1, paragraphs 1-2). In addition, individual transformed cells of a tumor acquire new mutations over time, resulting in clonal subsets with differential sensitivities to drugs, radiation, and immune attack (Vogelstein et al. (1993) Trends in Genetics, Vol. 9(4), page 141, column 1, paragraph 1). Thus, the skilled artisan recognized that substantial differences exist between different types of tumors that affect their response to different treatment modalities. In addition, cancer immunotherapy is further complicated by the fact that in order for the tumor antigen specific T cells to be effective against the tumor, the tumor must be able to express recognizable levels of peptide/MHC class I complexes derived from tumor antigen. At the time of filing, the art teaches that tumors evade immune responses by a variety of mechanisms including down-regulation of TAP and MHC-encoded proteasome components, loss of antigenic epitopes by either lack of expression or mutations, loss of functional β_2m expression , and loss of particular MHC class I alleles (Restifo et al (1993) J. Immunother., Vol. 14, page 183, col 1, lines 8-14, and page 184, col. 2). The loss or mutation of any of these molecules would inhibit the tumor cells from being recognized by effector immune cells. As a result of the

art recognized differences in tumor types, the skilled artisan would not have been able to correlate success in treating a glioma using IL-4 with the successful treatment of other types of tumors.

Further, in regards to the effects of different cytokines on different types of tumors, several references provide specific evidence that cytokines such as IL-4 , IL-10, GM-CSF, TNF-alpha, and interferon-gamma are not useful in generating therapeutic anti-tumor immune responses against non-CNS tumors. For examples, Bronte et al. demonstrates that the treatment of colon tumors in immunocompetent mice with recombinant virus encoding GM-CSF, interferon-gamma, or TNF-alpha, does not result in the inhibition of pulmonary metastases (Bronte et al. (1995) J. Immunol. Vol. 154, 5286-5292, see especially page 5287, Figure 4). Irvine et al. also teaches that the administration of IL-4, IL-10, GM-CSF or interferon-gamma do not induce antigen specific immunotherapy of tumors in vivo in immunocompetent mice (Irvine et al. (1996) J. Immunol., Vol. 156, 238-245, see especially page 241, column 2, paragraph 1, and page 243, column 1). Thus, the art of record supports the unpredictable effects of different cytokines on tumor therapy based on their different immunomodulatory properties, and particularly teaches the unpredictability of using IL-4, IL-10, GM-CSF, and interferon-gamma for generating anti-tumor immune responses against colon carcinomas.

Furthermore, at the time of filing, the skilled artisan did not consider gene therapy of cancer as either routine or predictable. Orkin et al., in particular, states in regards to cytokine-mediated cancer therapy that, "although several of these strategies show promise in mouse models, none has demonstrated efficacy in humans" (Orkin et al. (1995), "Report and Recommendations of the Panel to assess the NIH investment in research on gene therapy", 1-23,

page 6, paragraph 6). Vieweg et al. also states that, " in the presence of variable experimental data it will be difficult to predict the optimal cytokine and the optimal level of cytokine expression for human use." (Vieweg et al. (1994) Cancer Investigation, Vol. 13(2), 103-201, page 198, column 1, paragraph 1). Thus, based on the art recognized unpredictability of gene therapy using cytokines, the substantially different mechanisms and activities of individual cytokines, the lack of guidance provided by the specification for parameters affecting the delivery of any and all recombinant cytokine expressing HSV, the lack of correlation between applicant's working examples and the claims as written, and the breadth of the claims, the skilled artisan would not have been able to predict success in treating any and all types of tumors by administering a recombinant HSV which expresses only one $\gamma_1$34.5 gene product and which further expresses any cytokine without undue experimentation.

Applicant's arguments submitted in response to the previous grounds of rejection under 112, first paragraph, are addressed here in so far as they apply to the new grounds of rejection under 112, first paragraph, set forth above.

The applicant argues that while IL-10 and IL-5 are not effective in inhibiting the growth of gliomas, they are effective in inhibiting the growth of other tumor types. In support of this argument, that applicant submitted two abstracts, Kundu et al. and Masuda et al. Regarding Kundu et al., while Kundu et al. shows that transfection of a murine mammary tumor with IL-10 inhibits the growth of this tumor, there is no evidence that IL-10 would be expected to have a similar effect on any other type of tumor. In fact, as evidenced by Irvine et al., IL-10 does not have any anti-tumor effect against the CT26 colon carcinoma. As such, applicant's evidence

does not overcome the unpredictability in treating any type of tumor by expressing IL-10. In regards to the Matsuda et al. abstract, Matsuda et al. teaches that transfecting the CT26 colon carcinoma with the IL-5 gene can inhibit tumor growth. However, there is not teaching or suggestion in Matsuda et al. that such an effect on CT26 tumors could be extrapolated to any other cell type. Evaluation of the evidence as a whole, including the cited prior art, and the disclosure of the specification, makes clear that the skilled artisan was not able to predict without experimentation whether any particular cytokine would be effective against any particular tumor. In view of the breadth of the applicant's claims, such experimentation would be undue.

The rejection of claims 20-23 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of applicant's amendments to the claims.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 9:30-6:00 EST. If the examiner is not available, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735. For all official communications, **the new technology center fax number is (571) 273-8300**. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER